Preoperative albumin-to-alkaline phosphatase ratio is an independent prognostic factor for postoperative survival after gallbladder carcinoma radical surgery

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Research Article

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Abstract

Purpose: The relationships of the albumin-to-alkaline phosphatase ratio (AAPR) and the results in Gallbladder cancer (GBC) cases undergoing radical surgical process have been rarely discussed. The present work attempted to assess the prognosis implication of AAPR in GBC cases before operation.

Methods: We retrospectively selected 202 consecutive GBC cases treated from 2010 to 2017. Through univariate and multivariate studies, elements impacting overall survival (OS) and recurrence-free survival (RFS) were explored.

Results: Among the 202 cases, 93 (46%) achieved AAPR<0.4. The middle OS in cases with low AAPR before operation reached 26 months, less than that for high AAPR cases before operation (38 months, P<0.001). Low AAPR before operation displayed relationships to smaller surviving periods in univariate studies (HR, 2.738; 95%CI, 1.256-5.843; P<0.001). According to multivariate study, low AAPR cases achieved a lower OS (HR, 2.247; 95%CI, 1.483-3.404; P=0.028) and RFS (HR, 1.640; 95%CI, 1.037-3.210; P=0.041) than high AAPR cases.

Conclusion: AAPR is an independent indicator of poor prognosis in GBC patients after GBC radical surgery.

Highlights

1. patients with low AAPR, the overall survival was significantly shorter than those patients with high AAPR
2. AAPR provides a clinically applicable, economical, and non-invasive risk factor assessment tool to predict death from gallbladder cancer.[1]

Introduction

Gallbladder cancer (GBC) refers to the commonest malignant tumor of the biliary tract, taking up 80%-95% of biliary cancer cases [1]. CBG refers to the fifth commonest gastrointestinal tract malignancy, taking up ~1% of all cancers in our nation [2]. GBC prognosis remains ineffective for lack of effective diagnostic markers, single treatment choices, late diagnosis, and atypical symptoms [3]. GBC prognosis is primarily determined by the pathologic ascertainment of cancer tissue and distinguishing the pathologic type, classification, and stage of cancer for cases' prognosis. According to epidemiology-related research, the 3- and 5-years survival rates for cases having such illness reach 30% and 5%[4]. Accordingly, given the ineffective GBC prognosis, for this illness, other elements impacting patient survival should be identified.

Some prognostic models were developed and well-demonstrated in external verification groups. [5, 6]. Nevertheless, the prognosis implication of the mentioned models can be enhanced since none of them has been employed clinically for the waste of time and high cost of assays, insufficient standardization,

as well as non-reproducibility[7]. Accordingly, a novel prognosis element should be developed, being inexpensive and easy to detect in a normal way. Over the past few years, the albumin-to-alkaline phosphate ratio (AAPR), a new prognosis element, was proved noticeably related to more ineffective results for upper tract urothelial carcinoma (UTUC), cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC)[8-10]. Nevertheless, relevant studies were not conducted in GBC cases. Accordingly, this work attempted to assess the likely prognostic effect exerted by preoperative AAPR in cases GBC.

Patients And Methods

The present work conducted a retrospective study following the Helsinki Declaration and authorized by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University. The written consent of all subjects was acquired. Qualified cases were covered here based on: (1) cases with histological diagnosis of GBC; (2) GBC cases without other coexisting malignancies; (3) cases not receiving other treatments before being recruited; (4) cases with complete clinical data and available following up information: and (5) cases aged >18 years. The exclusion standard included: (1) cases with acute infection or chronic active inflammatory illness; (2) cases with collagen illnesses, anemia and other illnesses regarding the hematological mechanism; (3) cases undergoing anticoagulant treatment or albumin transfusions in advance to treating process; and (5) cases with perioperative surgical-correlated mortality. Clinical information in 30 days before surgical process for 202 of the cases were covered. All cases took radical operation for CBG for 2010-2017 at the Second Affiliated Hospital, Wenzhou Medical University. 1 time a year, the cases were connected via phone, and their recent physical state was acquired. The data of following-up was from surgical information to death date or final contact, or the end of November 2019. Overall survival (OS) was the date from the surgical process to death or the last following-up. Recurrence free survival (RFS) was computed according to the date of surgery till the initial relapse or death for certain reasons, or to the date of last following-up.

Clinical information

The medical information below were harvested from the cases in the hospital in a retrospective manner: TNM staging, pathologic data (tumor lymph node metastasis, tumor size, tumor differentiation), serum carcinoembryonic antigen (CEA), serum CA19-9, neutrophil-to-lymphocyte ratio (NLR), alkaline phosphatase (ALP), serum albumin (ALB), hemoglobin, BMI, age, and gender (The United States Joint Committee on cancer [7th edition], staging of gallbladder cancer). By electrochemiluminescence immunoassays (Cobas; Roche Diagnostics, Germany) performed at the Clinical Laboratory Department, Second Affiliated Hospital of Wenzhou Medical University, China, Serum CA19-9 and CEA levels were ascertained. The normal reference values following an existing study include: GNRI<100, NLR<2.6, CA19-9≤37U/mL, CEA≤5ug/L[11]. The cutoff value of AAPR was ascertained by a ROC analysis to assess OS, and 0.40 was taken as the final cutoff value for its maximal Youden index. The radical resection is defined that the major tumor is eliminated jointly with the affected tissue and the metastatic lymph nodes. (For the T1 a GBC, we performed a simple cholecystectomy following a laparotomy or laparoscopic surgical process. In terms of the T1b GBC, an extended cholecystectomy was applied. For

cases with GBC in stage T2 or over, an extended cholecystectomy was often carried out. For the extended cholecystectomy, we could carry out the gallbladder bed wedge resection or IVb/V liver resection under the intraoperative condition. The scope of lymph node dissection is required to cover the posterior superior pancreaticoduodenal lymph node, the lymph nodes around the hepatoduodenal ligament [the hepatic artery and portal vein lymph nodes], the common bile duct lymph node, as well as the cystic duct lymph node. According to the tumor pathology, no tumor tissue exists at the margin.

Statistical method

For category-related parameters, by the Fisher's exact test or chi-squared test, noticeable differences were assessed. In terms of continuous information, with the independent-sample t-test or Mann-Whitney test, the comparison was drawn about mean difference. For testing the associations between parameters and OS, multiple-variate and univariate Cox proportional hazard modes were adopted. By calculation, OS appeared to be the period between surgery and death due to any reason or the last following-up. With the Kaplan-Meier approach, survival curves were comparatively studied by the log-rank test. A p-value<0.05 was found with statistics-related significance. Statistical studies were carried out with SPSS version 22 (SPSS, Lnc., Chicago, IL, USA).

Results

Baseline characteristics

A total of 202 cases suffering GBC were recruited, the mean age was 68.54±11.02 years, 68.3% were female, and the mean AAPR reached 0.40±0.22. Furthermore, 46% cases had low AAPR with GBC according to diagnosis. Table 1 lists the fundamental features of survivor and non-survivor cases. Compared with survivor cases, non-survivor cases were older, with lower BMI, hemoglobin, albumin and AAPR. Between the survivor and non-survivor cases, large CA19-9 (P<0.001) and large CEA (P=0.006) were noticeably different. In terms of tumor characteristics, lymph node metastasis (P=0.046), tumor differentiation (P<0.001), advanced TNM stage (P<0.001) and advanced infiltration depth T (P<0.001) noticeably impacted the death of GBC. Moreover, the AAPR was conducive to splitting participants into two groups, group with high AAPR (n=109), and group with low AAPR (n=93) (Table 2). In contrast to high AAPR cases, the low AAPR cases were older, with lower hemoglobin, albumin. Higher ALP, NLR (P<0.001), CA19-9 (P=0.028), CEA (P=0.029), incidence of gallstones (P=0.048), advanced infiltration depth T (P=0.033), advanced TNM stage (P=0.099) and larger tumor size (P=0.009) evidently impacted low GNRI levels.

Kaplan-Meier survival analysis

Of the 202 cases, 94 died, and 108 continued to live. In terms of the OS (P<0.001) (Fig. 1) and RFS (P<0.001) (Fig. 2), the prognosis was noticeably worse in cases exhibiting low AAPR levels than in cases with high AAPR levels. Cases in the high AAPR level group developed a middle OS time of 38 months (95% CI 28.35-47.94), and those in the low AAPR group developed a middle OS of 26 months (95% CI

21.03-30.97). The recurrence rate during following-up here reached 52.0% (105 cases), and the middle illness -free survival in this series reached 24 months. The middle RFS was noticeably smaller in the low AAPR group than in the high AAPR group (12months and 35 months, separately; P<0.01).

Univariate and multivariate analysis

Table 3 lists the OS-relevant parameters when GBC radical surgical process is completed in line with univariate and multivariate Cox proportional hazard modes. For the univariate study, age, serum CA19-9>37, CEA>5, hemoglobin level, lymph node metastasis, TNM III+IV, ineffective differentiation, invasive depth III+IV, GNRI<100, AAPR<0.4 exhibited relationships to low OS. In line with the results of multivariate analysis, age (HR, 1.030, 95%CI, 1.001-1.061; P=0.047), hemoglobin (HR, 1.040, 95%CI, 1.000-1.049; P=0.043), ineffective differentiation (HR, 2.073, 95%CI, 1.081-4.381; P=0.031), TNM III+IV (HR, 7.853, 95%CI, 1.648-37.421; P=0.010), GNRI (HR, 2.312, 95%CI, 1.119-4.777; P=0.024) and AAPR (HR, 2.247, 95%CI, 1.483-3.404; P=0.028) adversely influenced OS. Table 4 lists a multiple-variate and univariate Cox proportional hazard regression mode in terms of RFS. Multivariate analysis identified three adverse prognosis elements, lymph node metastases (HR, 2.605, 95%CI, 1.163-6.896; P=0.026), GNRI (HR, 4.881, 95%CI, 2.367-10.063; P<0.001) and AAPR (HR, 1.640, 95%CI, 1.037,3.210; P=0.041), which affect RFS.

Prognosis implication of AAPR

To compare the predictability of the mortality and recurrence rate among GBC cases, ROC curves of ALP, albumin, AAPR were drawn (Fig 3). AAPR displayed the maximal area under the ROC curves, with statistical significance (AUC=0.706 for mortality, 95%CI, 0.633-0.779; P<0.001, AUC=0.711 for recurrence rate, 95%CI, 0.641-0.781; P<0.001). The optimal cutoffs of GNRI for predicted mortality and recurrence rate reached 0.40 and 0.41 separately.

Discussion

Here, the prognosis-related implication of AAPR in GBC cases taking surgical process was ascertained. This is the first study ascertaining the relationships of AAPR to GBC. As revealed from the results here, AAPR levels under 0.40 showed down-regulated OS and RFS.

Anthony et al. initially reported AAPR in 2015. These researchers suggested AAPR a single prognosis-related index for hepatocellular carcinoma (HCC) exhibiting the maximal c-index and X^2 compared with other liver biochemical variables[9]. Existing studies subsequently proved that AAPR was another single index of advanced HCC and metastatic nasopharyngeal carcinoma; its capability for prediction noticeably outperform ALB or ALP only[12, 13]. Over the past few years, Xiong and colleagues indicated that AAPR displayed noticeable associations with worse survival results in CCA cases[9]. Given its higher predicting accuracy in terms of cancer results and lacked researches assessing the prognosis implication effect in GBC cases, this present research was carried out, reporting the consistent outcomes with the previous ones. As shown in Fig 3. AAPR developed the maximal area under ROC curve in contrast to ALB and ALP, with statistical significance.

The reason for lower AAPR elevating the mortality and risk of tumor relapses is still not clear; nevertheless, a likeability requires to be tackled down: AAPR is computed from serum ALB concentration split by serum ALP level, revealing that systemic inflammatory and response nutritional deficiency were likely to impact GBC developing and progressing processes if AAPR prognostically predicts tumor metastasis and recurrent process. Note that ALB is fabricated by liver, in which it acts more than a vital nutritional indicator, while relating to systemic immunological responses to inflammation or tumors[13]. ALB is capable of making cell proliferation and growth stable, modulating immune reactions, and resist being oxidized by carcinogens[14]. Accordingly, low ALB is likely to impair immunity and ineffective anti-cancer responses[15]. Existing research indicated that ALB was a feasible predicting tool in a range of cancers, covering HCC, CCA and prostate cancer[16-18]. ALP refers to a hydrolase enzyme largely existing in bones, livers, and kidneys. Serum ALP conditions are generally up-regulated in cases with HCC, kidney illness, as well as bone metastasis[12]. Moreover, ALP was found single risk element of a range of cancers (e.g., CCA and HCC)[19-21].

Here, compared with cases exhibiting large AAPR before surgery, cases exhibiting ineffective AAPR exhibited larger NLR (P<0.001), CA19-9 (P=0.029), TNM stage(P=0.009), tumor size (P=0.009), advanced infiltration depth T (P=0.033), incidence of gallstones (P=0.001). Accordingly, cases exhibiting ineffective AAPR could present tumor developing process. For this reason, such variable is likely to be a conducive index of tumor malignancy with high grades. Nevertheless, the conclusion is not likely to be drawn here that low AAPR is probably leading to or attributed to tumor malignancy.

Furthermore, low AAPR, high age, low hemoglobin, ineffective differentiation, low GNRI and TNM III+IV, were ascertained as independent prognosis elements in cases with GBC by multivariate study. According to the knowledge of the authors, this analysis initially reports that a preoperative low AAPR acts as a predicting and prognosis element of GBC. Furthermore, we find that cases with low AAPR, the OS and RFS was noticeably smaller than those cases with high AAPR. Accordingly, cases with GBC and low AAPR are highly likely to die and suffer from recurrent disease even after curing operational process. For this reason, the mentioned cases are likely to require more rigorous following-up when the surgical process is completed.

Here, according to the largest Youden index value, the most superior cutoff was acquired by ROC study. The optimal cutoffs of AAPR for assessed mortality and recurrence rate reached 0.40 and 0.41 separately, that was close to that of non-metastatic renal cell carcinoma and CCA study[9, 22]. Note that the cutoff-point did not abide by HCC and non-small-cell lung cancer[8, 23]. Some perspectives should be considered involve: the utilization in a range of cancer, groups exhibiting a range of sizes of the sample, following-up periods and assaying approaches for AAPR. Accordingly, in-depth analyses should be conducted for identifying the optimal cutoff value in line with specific cancers.

This study exhibits several limiting points. First, the single-center property and retrospective design were major limitations. Regardless of rigorous adherence to inclusion and exclusion standards, selection bias might remain in the present retrospective work. Second, the cut-off AAPR values may not be the best, and

external verification is still required. Third, the absence of verification groups caused the failed verification of AAPR as an independent factor for GBC subjects. AAPR refers to a ratio of ALB and ALP, the low level of which may present the conditions of formation of invasive cancer, malnourishment, liver failure as well as inactive immune response, all of which might display relationships to the ineffective prognosis of GBC. More fundamental study and prospective research are required for delving into the molecular mechanism underpinning the relationships between AAPR and prognostic process.

Conclusion

To sum up, there outcomes revealed that AAPR is a likely prognosis-related index in GBC subjects taking surgical process. Considering its prognostic power, usability and low cost, AAPR should be covered in subsequently works and clinical trials. Nevertheless, larger scale, multi-center studies should be conducted for in-depth verification.

Declarations

Conflicts of interest

The authors declare no potential conflicts of interest.

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Author Contributions Statement

JX– study concept and design; preparation, review and approval of manuscript. DZ and TW– data collection and interpretation; preparation, review and approval of manuscript. JX ,DZandTW – preparation, review and approval of manuscript.

Ethics approval and consent to participate

This study has obtained the approval from the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (No. LCKY2017-21) and has obtained the written informed consent of all

subjects following the Declaration of Helsinki.

Availability of data and materials

The data that support the findings of this study are available from Institutional Review Board of the second affiliated hospital and Yuying Children's Hospital of Wenzhou Medical University but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Institutional Review Board of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University.

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Tables

Table 1. The comparison of the clinical and pathologic between survivors and non-survivors groups.

	overall	Survivors	Non-survivors	P value
Case n (%)	202	108	94	
Age, years	68.54±11.02	66.81±10.87	70.52±13.91	0.017
Female (%)	68.3%	70.4%	66.0%	0.546
Height, cm	159.56±7.44	159.39±7.69	159.76±7.16	0.728
Weight, kg	58.31±9.87	56.42±8.96	59.96±10.36	0.011
BMI, kg/m^2	22.87±3.29	23.58±3.53	22.05±2.80	0.001
GNRI	100.08±10.69	104.12±9.80	95.44±9.78	<0.001
AAPR	0.40±0.22	0.46±0.20	0.33±0.22	<0.001
Hemoglobin mean, g/L	124.94±17.97	127.12±14.43	122.43±21.13	0.044
Serum albumin mean, g/L	38.30±5.18	40.10±4.19	36.23±5.44	<0.001
NLR				0.112
<2.6	61.4%	66.7%	55.3%	
≥2.6	38.6%	33.3%	44.7%	
Serum CA19-9 (U/mL)>37				<0.001
No	58.9%	72.2%	43.6%	
Yes	41.1%	27.8%	56.4%	
Serum CEA level (ng/mL) >5				0.006
No	77.5%	86.0%	67.5%	
Yes	22.5%	14.0%	32.5%	
T (%)				<0.001
I-II	34.9%	48.0%	20.9%	
III-IV	65.1%	52.0%	79.1%	
Gallstones (%)				0.077
No	39.9%	46.1%	33.0%	

Yes	60.1%	53.9%	67.0%	
Tumor size (cm) >3 (%)				1.000
No	53.2%	53.6%	52.9%	
Yes	46.8%	46.4%	47.1%	
Differentiation of GBC (%)				<0.001
Poor/unknown	37.4%	24.2%	52.5%	
Well/moderate	62.6%	75.8%	47.5%	
TNM stage (%)				<0.001
I-II	30.5%	46.2%	12.8%	
III-IV	69;.5	53.8%	87.2%	
Lymph node metastases (%)				0.046
No	75.3%	80.8%	69.2%	
Yes	24.7%	19.2%	30.8%	
GNRI				<0.001
≥100	49.0%	68.5%	26.6%	
<100	51.0%	31.5%	73.4%	
AAPR				<0.001
≥0.4	54.0%	66.1%	33.9%	
<0.4	46.0%	38.7%	61.3%	

Table 2 Clinical and pathologic characteristics of the 202 study patients.

	overall	High AAPR (≥0.4)	Low AAPR (<0.4)	P value
Case n (%)	202	109 (54%)	93(46%)	
Age, years	68.54±11.02	67.06±11.53	70.28±10.17	0.038
Female (%)	68.3%	77.8%%	59.2%	
BMI, kg/m^2	22.87±3.29	23.16±3.08	22.52±3.51	0.168
Hemoglobin mean, g/L	124.94±17.97	127.91±18.65	121.45±16.56	0.011
Serum albumin mean, g/L	38.30±5.18	40.13±4.40	36.16±5.21	<0.001
ALP, U/L	162.71±200.07	73.85±17.34	266.85±258.43	<0.001
NLR				<0.001
<2.6	61.4%	72.5%	48.4%	
≥2.6	38.6%	27.5%	51.6%	
Serum CA19-9 (U/mL)>37				<0.001
No	58.9%	72.8%	42.1%	
Yes	41.1%	27.2%	57.9%	
Serum CEA level (ng/mL) >5				0.029
No	77.5%	84.0%	69.6%	
Yes	22.5%	16.0%	30.4%	
T (%)				0.033
I-II	34.9%	41.7%	26.7%	
III-IV	65.1%	58.3%	73.3%	
Gallstones (%)				0.001
No	39.9%	50.9%	26.4%	
Yes	60.1%	49.1%	73.6%	
Tumor size (cm) >3 (%)				0.009
No	53.2%	62.5%	40.9%	
Yes	46.8%	37.5%	59.1%	
Differentiation of GBC (%)				0.429
Poor/unknown	37.4%	34.4%	41.0%	
Well/moderate	62.6%	65.6%	59.0%	

TNM stage (%)				0.009
I-II	30.5%	38.5%	20.9%	
III-IV	69;.5	61.5%	79.1%	
Lymph node metastases (%)				0.400
No	75.3%	77.9%	72.1%	
Yes	24.7%	22.1%	27.9%	

Table 3 Univariate and multivariate analyses of prognostic factors with overall survival.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95% CI)	P-value
Age	1.026 (1.006-1.046)	0.009	1.030 (1.001-1.061)	0.047
Sex male	1.195 (0.779-1.832)	0.414		
serum CA 19-9(U/mL)>37	2.304 (1.470-3.612)	<0.001		
Serum CEA (ng/mL) >5	1.904 (1.192-3.041)	0.007		
Hemoglobin	1.192 (1.098-1.214)	0.038	1.040 (1.000-1.049)	0.043
NLR >2.6	1.447 (0.963-2.174)	0.075		
Gallstones	1.271 (0.821-1.970)	0.282		
Tumor size >3cm	1.021 (0.639-1.633)	0.930		
T III-IV	1.630 (1.253-2.121)	<0.001		
Poor differentiation	2.323 (1.496-3.607)	<0.001	2.073 (1.081-4.381)	0.031
Lymph node metastases	1.567 (1.004-2.448)	0.048		
TNM stage III+IV	3.688 (2.011-6.764)	<0.001	7.853 (1.648-37.421)	0.010
GNRI<100	3.656 (2.308-5.790)	<0.001	2.312 (1.119-4.777)	0.024
AAPR<0.4	2.738(1.256-5.843)	<0.001	2.247(1.483-3.404)	0.028

Table 4 Univariate and multivariate analyses of prognostic factors associated with RFS.

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95% CI)	P-value
Age	1.016(0.998-1.034)	0.074		
Sex male	0.808(0.539-1.210)	0.301		
serum CA 19-9(U/mL)>37	1.928(1.263-2.945)	0.002		
Serum CEA (ng/mL) >5	1.631(1.025-2.593)	0.039		
Hemoglobin	0.994(0.982-1.006)	0.306		
NLR >2.6	1.527(1.036-2.251)	0.032		
Gallstones	1.506(0.995-2.279)	0.053		
Tumor size >3cm	0.892(0.570-1.396)	0.617		
T III-IV	1.112 (0.904-1.368)	0.314		
Poor differentiation	1.640(1.084-2.484)	0.019		
Lymph node metastases	3.318 (1.128-7.048)	0.014	2.605(1.163-6.896)	0.026
TNM stage III+IV	1.617 (1.037-2.520)	0.034		
GNRI<100	5.395 (3.421-8.508)	<0.001	4.881(2.367-10.063)	<0.001
AAPR<0.4	2.507(1.691-3.718)	<0.001	1.640(1.037-3.210)	0.041

Figures

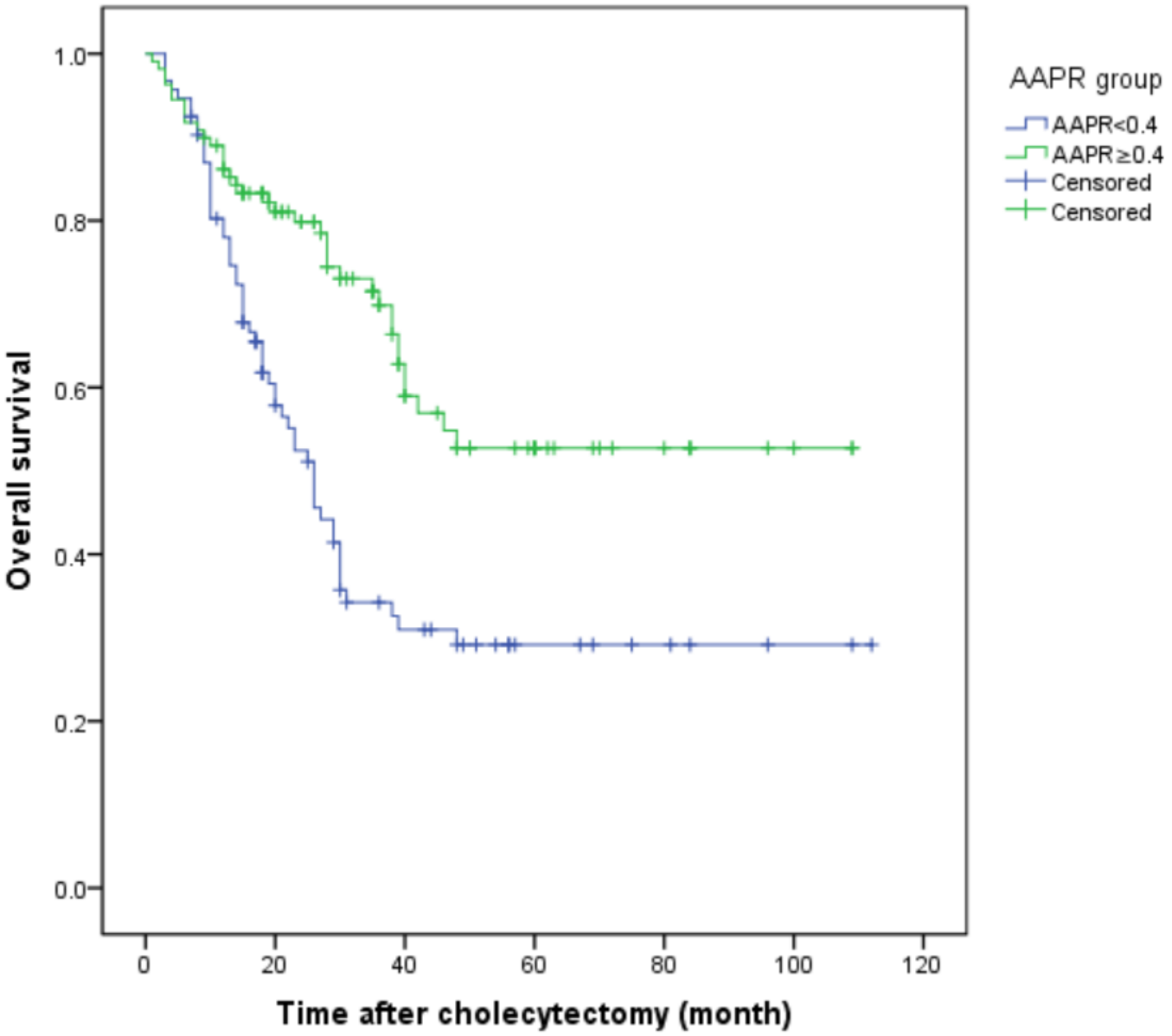

Figure 1

The overall survival rate of GBC patients after GBC radical surgery

Notes: The Kaplan-Meier curve showed significant difference in the probability of total survival after GBC radical surgery in patients with preoperative high AAPR and low AAPR levels. P<0.001 (log-rank test)

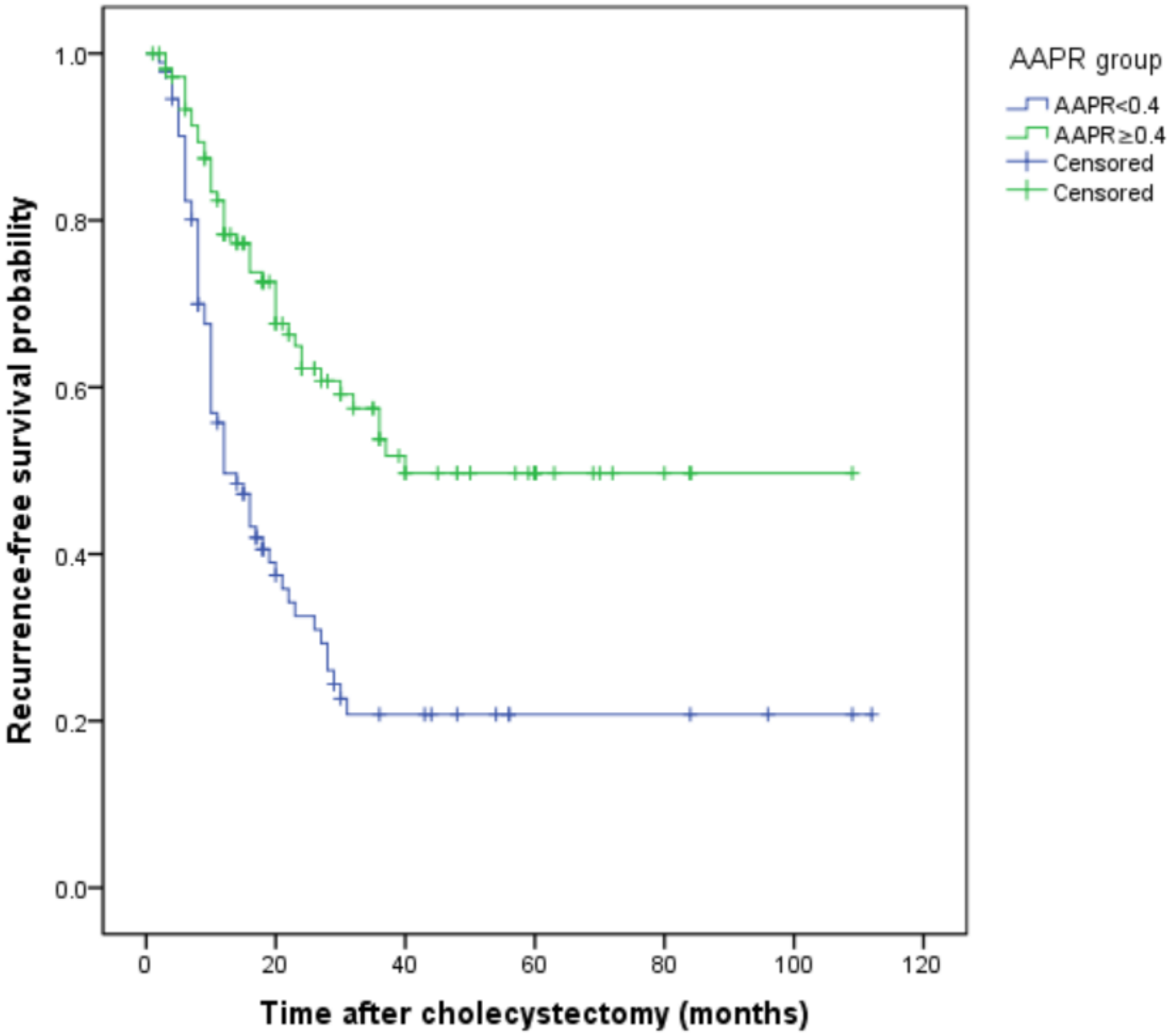

Figure 2

RFS of patients with GBC after GBC radical surgery.

Notes: Kaplan-Meier curves show significant difference in RFS probability after GBC radical surgery in patients with preoperative high AAPR and low AAPR levels. P<0.001 (log-rank test).

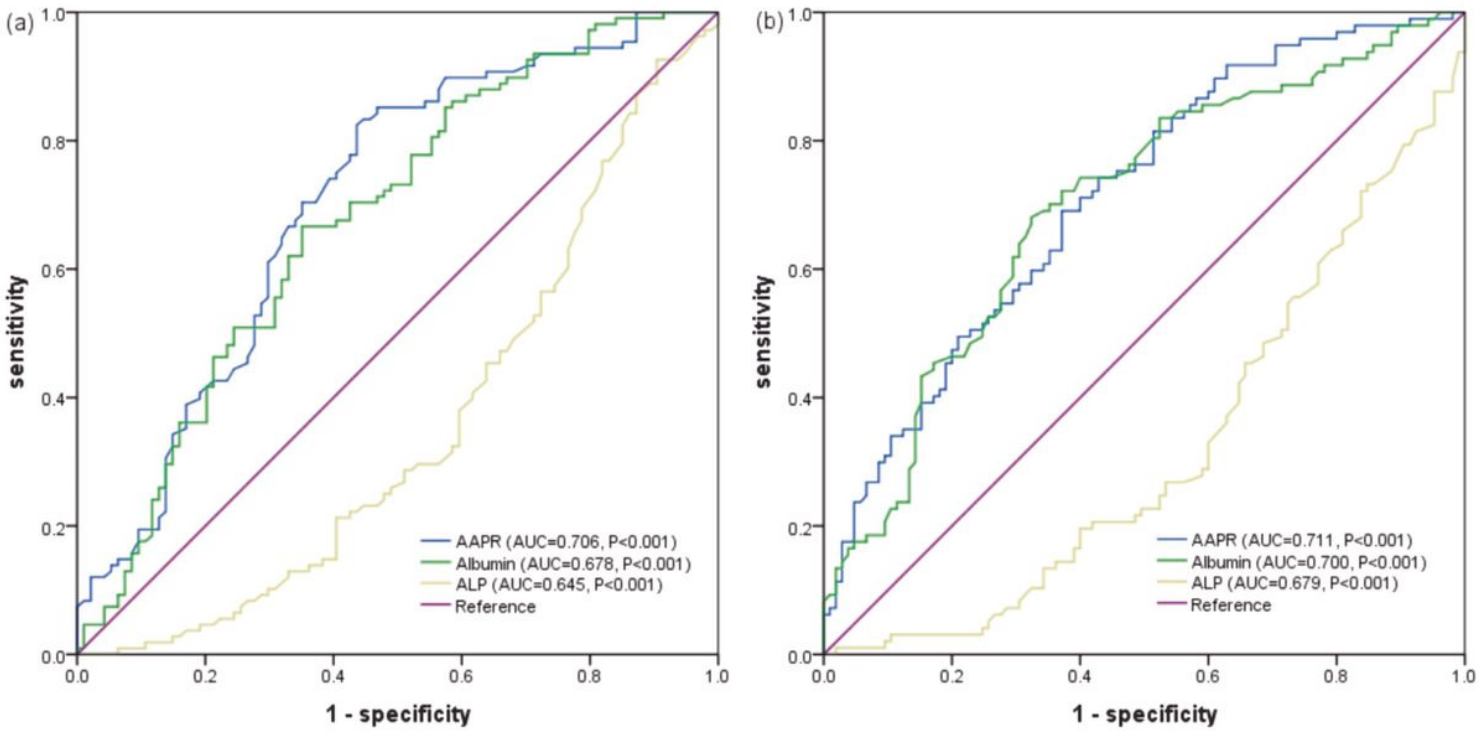

Figure 3

(a) Receiver operating characteristic curve analysis based on AAPR, albumin and BMI for overall survival
(b) Receiver operating characteristic curve analysis based on AAPR, albumin and BMI for RFS.